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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,157	JOSEL ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-39* is/are rejected.

7)☒ Claim(s) *37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (i.e., see 2/24/06 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/7/05 has been entered (e.g., see 12/7/05 Declaration by Dr. Mrksich). Claims 33-39 were pending. No claims were amended, added or canceled. Therefore, claim 33-39 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are withdrawn in view of Applicants' arguments and/or declaration.

New Rejections and Objections

Objections to the Claims

3. Claim 37 is objected to because of the following informalities:

A. Claim 37 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form. Claim 37 depends from

claim 36. Claim 36 recites in part: "protecting groups." Claims 37 recites the limitation acid-labile and acid-stable protecting groups, which would encompass "all" protecting groups. Therefore, claim 37 does not further limit claim 36.

Claim Rejections - 35 USC § 112, second paragraph

4. Claim 34, 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 34 and 36** recite the limitation "the reactive side groups" wherein there is no antecedent basis for the "side" portion of this limitation in the claim. Therefore, claims 34, 36 and all dependent claims are rejected under 35 USC 112, second paragraph.

Claim Rejections - 35 USC § 103

5. Claims 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst et al. (Bredehorst, R.; Wemhoff, G. A.; Kusterbeck, A. W.; Charles, P. T.; Thompson, R. B.; Ligler, F. S.; Vogel, C.-V. "Novel Trifunctional Carrier Molecule for the Fluorescent Labeling of Haptens" *Analytical Biochemistry* **1991**, *192*, 272-279) and Brinkley (Brinkley, M. "A brief Survey of Methods for Preparing Protein Conjugates with Dyes, Haptens and Cross-linking Reagents" *Bioconjugate Chem.* **1992**, *3*, 2-13) and Yang (Yan, S.; Niu, J. "Solid phase synthesis of the A-chain of insulin and its recombination with the B-chain to crystalline insulin" Shengwu Huazue Yu Shengwu Wuli Xuebao **1992**, 24(5), 497-502) (please note that a translation will be provided when it becomes available).

For ***claim 33***, Bredehorst et al. (see entire document) teach a method for the synthesis of novel trifunctional carrier for the fluorescence labeling of haptens (e.g., see abstract), which reads on the claimed invention. For example, Bredehorst et al. teach the use of a linear peptide carrier (e.g., see Bredehorst, page 275, figure 1 showing "insulin A-chain" carrier). In this scenario, the first two amino acids (or, alternatively, any other length less than 19 e.g., the first three, first four, etc.) of the insulin chain represent the linear carrier. That is, at least two amino acids have been "linked" together to form a linear chain. Consequently, any of the remaining amino acids (i.e., 21 – first two, 21 – first three, 21 – first four, etc. wherein "21" is the "total" length of the insulin A-chain shown if figure 1 on page 275) represent "additional" amino acids to which the DNP hapten molecule and two remaining DNP molecules are covalently attached through either the terminal Gly or hydrazine linkers respectively (e.g., see page 275, figure 1 showing attachment of 1 DNP and 2 Fl groups bound to the Glu residues). For example, in one alternative interpretation one DNP hapten and one Fluorescein group are attached to the carrier (i.e., Asn→ Gln) via a Gly-Ile-Val-Glu "additional" tetrapeptide (i.e., the carrier is viewed as being the insulin A-chain without the Gly-Ile-Val-Glu tetrapeptide, instead of the insulin A-chain in its entirety). Thus, in this scenario, four "additional" amino acids have been "introduced" to the Asn→ Gln peptide. Please note that Applicants' use of "comprising" language does not preclude the addition of additional groups to the linear carrier. Furthermore, the claims do not require that the hapten/luminescent groups be bound to the amino acid side chains. The claims merely require that these groups bind to "amino groups, thiol groups, and a combination thereof"

(e.g., see claim 33). Thus, the examiner has interpreted these claims as not excluding the use of linker molecules like hydrazine as long as "additional" amino acids have been added to the carrier and the hapten/luminescent groups are covalently attached (through the linker) to the linear carrier. Bredehorst et al. also disclose defining reproducible distances between the hapten and DNP groups (e.g., see figure 1 wherein three fluorescein molecules are disclosed; see also page 273, column 1, paragraph 1, "The sites for fluorophores attachment are 4, 17, and 21 amino acids away from the hapten attachment site"; see also page 277, column 2, paragraph 1, The backbone of the carrier is the A-chain of insulin which provides several essential features, including ... (c) sufficient length between the label attachment sites to prevent self-quenching of the fluorophores, (d) sufficient length between the hapten and the label attachment sites to limit both interference by the fluorophores with antibody binding to the hapten and quenching of the fluorophores due to interaction with the hapten"). In addition, Bredehorst et al. disclose that the conjugate comprising a minimum of 5 and a maximum of 100 amino acids (e.g., see figure 1, DNP-Ins-Fl wherein 21 amino acids are disclosed). Finally, Bredehorst et al. disclose the use of "amino" groups for binding the haptens (e.g., the N-terminus) and fluorescein molecules (e.g., via a hydrazine linker) (e.g., see Bredehorst et al., figure 1; see also Methods section, especially page 273, column 1, Synthesis of DNP-Ins-FL section).

For ***claim 35***, Bredehorst et al. teach the use of an N-terminal primary amine to link the hapten to the carrier (e.g., see Bredehorst et al., figure 1).

The prior art teachings of Bredehorst et al. differ from the claimed invention as follows:

For ***claim 33***, Bredehorst et al. fail to teach the use of solid-phase synthesis (see Bredehorst et al., page 273, column 1, last paragraph wherein Bredehorst et al. purchased the insulin carrier from Sigma and thus the reference is silent as to whether or not the insulin was produced via solid-phase synthesis). In addition, Bredehorst et al. fail to teach the use of luminescent metal chelates as marker molecules. Bredehorst et al. only teach the use of fluorescein markers instead (e.g., see Bredehorst et al., figure 1).

For ***claim 34 and 36-37***, Bredehorst et al. do not teach the use of "protecting groups" in conjunction with the reactive side groups.

For ***claims 38-39***, Bredehorst et al. do not teach the use of the haptens listed therein (e.g., see claims 38-39). Bredehorst et al. only teach the use of 2,4-dinitrophenol (e.g., see abstract).

However, the combined references of Brinkley, Yang and Massey et al. teach the following limitations that are deficient in Bredehorst et al.:

For ***claim 33***, the combined references of Brinkley, Yang and Massey et al. (see entire documents) teach the use of solid-phase synthesis to make peptides like the insulin carrier disclosed by Bredehorst et al. (e.g., see Yang et al., abstract wherein insulin A-chain was produced using solid-phase synthesis). In addition, the combined references of Brinkley, Yang and Massey et al teach the use of metal chelates for labeling haptens (e.g., see Massey et al., abstract, see also claim 11, "A method according to claim 1, wherein the reagent comprises an electrochemiluminescent chemical moiety conjugated

to an ... hapten ... or biotin"; see also claims 15-20 wherein bipyridine chelators are disclosed).

In the alternative that Bredehorst et al. additionally fail to teach the use of 1-10 additional amino acids as "linker" molecules for the attachment of metal chelates or, alternatively, the hapten molecule (which is not the case, see above). For the sake of argument, the Examiner notes that the combined references of Brinkley, Yang and Massey et al. also teach this limitation (e.g., see Brinkley, section II.A. wherein the use of amino acids linker molecules with reactive "amino groups" such as lysine for the attachment of haptens and fluorophores to a conjugate (e.g., Brinkley, section II.A.).

For ***claims 34 and 36-37***, the combined references of Brinkley, Yang and Massey et al. (see entire documents) teach the use of protecting groups (e.g., see Brinkley, page 2, column 2, paragraph 1, "in these molecules, the N-terminal amino group is N-acylated [i.e., protected]"; see also Yang, abstract, disclosing "tert-Bu" group for side chain protection and TFA for "selective" side chain removal).

For ***claim 35***, the combined references of Brinkley, Yang and Massey et al. (see entire documents) also teach the use of primary amines including the ϵ-amine of lysine (e.g., see Brinkley, page 2, column 1, last paragraph).

For ***claims 38-39***, the combined references of Brinkley, Yang and Massey et al. teach the use of hapten molecules like digoxin and theophyllin (e.g., see figures 6 and 7; see also Examples 32-34).

It would have been *prima facie* obvious to one skilled in the art at the time the invention to synthesize the peptide carrier molecule as disclosed by Bredehorst et al. on a

solid-support as disclosed by Yang because Yang developed a solid-phase method for this exact purpose i.e., they developed a solid-phase method for the synthesis of the insulin A-chain (e.g., see Yang, abstract). Furthermore, a person of skill in the art would have been motivated to use solid-phase synthesis to obtain high yields of the purified insulin product using the facile washing procedures associated with the solid-phase process. Finally, a person of skill in the art would reasonably have expected to be successful because Yang explicitly state that they can produce the insulin A-chain on a solid-support using an Fmoc protection strategy (e.g., see Yang et al., abstract) and Bredehorst et al. teach how this insulin chain can be further derivatized once it is produced (e.g., see .

Furthermore, it would have been *prima facie* obvious to substitute the metal chelates (e.g., see claims 15-20) disclosed by Massey et al. for the fluorescein molecules disclosed by Bredehorst et al. because Massey et al. explicitly state that these metal chelates can be used to label haptens, which would encompass the 2,4-dinitrophenol (DNP) hapten disclosed by Bredehorst et al. (e.g., see claim 11, "A method according to claim 1, wherein the reagent comprises an electrochemiluminescent chemical moiety conjugated to an ... hapten"). Furthermore, a person of skill in the art would have been motivated to use such metal chelates because Massey et al. explicitly states that their metal chelates are useful for immunoassays (e.g., see figures 1, 6 and 7; see also Summary of Invention; see also paragraph bridging pages 25-26), which would encompass the immunoassays disclosed by Bredehorst et al. (e.g., see Bredehorst et al., page 272, column 2, last paragraph). In addition, Massey et al. state that their metal

chelates are "highly diagnostic of the presence of a particular label, sensitive, non-hazardous, inexpensive, and can be used in a wide variety of applications" (e.g., see Massey et al., page 5, paragraph 1; see also Examples 36 and 37). Finally, a person of skill in the art would have reasonably expected to be successful because Massey et al. state that their metal chelates "can be used in a wide variety of applications" (e.g., see Massey et al., page 5, paragraph 1) wherein the labeling of haptens represents a "preferred embodiment" (e.g., see Massey et al., claim 11; see also figures 1, 6 and 7; see also Examples; see also page 7). Massey et al. also state, "Extensive work has been reported on methods for detecting Ru(2,2'-bipyridine)$_3^{2+}$ using photoluminescent, chemiluminescent, and electrochemiluminescent means", which shows that the art is not new and unpredictable (e.g., see Massey et al., page 7, last paragraph; see also page 32, lines 26-29 wherein Massey explicitly state that said metal chelates can be conjugated to haptens, "In one embodiment of the invention the reagent is a electrochemiluminescent chemical moiety conjugated to an ... hapten").

Finally, it would have been *prima facie* obvious at the time the invention was made to use amino acid linkers, such as lysine, to attach the metal chelating groups disclosed by Massey et al. to the carrier peptide as disclosed by Bredehorst et al. because the method of attachment represents a mere design choice that was well known in the art (e.g., see Brinkley, entire document, reviewing various methods that were "standard" in the art for attaching haptens and/or labels to a carrier; see especially section II.A. wherein the use of lysine "handles" are disclosed). Furthermore, Brinkley explicitly state that amine-probes like lysine can be used to attach haptens like the DNP disclosed by

Bredehorst et al. (e.g., see Brinkley, page 10, column 1, paragraph 2, "The following general procedure is ... adaptable to amine-reactive ... hapten"). A person of skill in the art would have been motivated to use lysine as linker for the attachment of the haptens and/or metal chelates because said lysine can be easily incorporated into a peptide and/or protein through synthesis and/or genetic manipulation (e.g., Brinkley, page 2, column 1, last full paragraph) and are "... reasonably good nucleophiles ... and therefore react easily and cleanly with a variety of reagents to form stable bonds" (e.g., see Brinkley, page 2, last paragraph). Finally, a person of skill in the art would have reasonably expected to be successful because Brinkley state that the ϵ-amine of lysine is "one of the most common" reactive groups employed to link haptens and/or marker molecules to a protein conjugate (e.g., see Brinkley, page 2, last paragraph). In addition, Bredehorst et al. explicitly show that a hapten like 2,4-dintrophenol (DNP) can be linked to a marker molecule using lysine (e.g., see figure 1, compound DNP-Lys-Fl; see also page 278, column 1, first full paragraph, "In principle, labeling of a hapten with multiple fluorophores is fairly simple. Polyamines such as polylysine ... are suitable").

Response

6. To the extent that Applicant's arguments directed to the previous 35 U.S.C. § 103(a) rejection can be applied by analogy to the above rejection, the following comments are noted:

[1] Applicants argued, "Merrifield teaches a method of solid phase synthesis – but fails to teach host to form a conjugate –especially a conjugate where the hapten, metal chelates or biotin

are attached to the polypeptide via the side chains of amino acids" (e.g., see 2/24/06 Response, pages 2 and 3, especially, page 3, paragraph 2).

[2] Applicants also set forth the Mrksich declaration a n note especially paragraph 19 (e.g., see 2/24/06 Response, pages 3 and 4; see Mrksich declaration, especially, paragraph 19).

[3] Applicants argue, "The examiner cites Bredehorst for teaching a method for the synthesis of a linear peptide carrier ... [however] the authors did not use insulin because it was an ideal carrier – since one of the positions for fluorophores attachment was sufficiently close to the hapten to promote quenching-but rather because it was readily available ... had the authors appreciated that solid phase synthesis could be used to prepare the carrier, the would have done so ... Hence I find that the Bredehorst reference ... does not-either directly or indirectly-teach the use of solid-phase synthesis to prepare the oligomeric carrier molecules" (e.g., see Mrksich Declaration, paragraph 12; see also page 5, paragraph 17 wherein the argument is repeated).

[4] Applicants argue, "None of these references, however, refers to solid-phase synthesis of a carrier from amino acids that are covalently bound to labels or haptens" (e.g., see Mrksich Declaration, paragraph 13).

[5] Applicants argue, "The protecting group [in Merrifield] is not incorporated in order to permit the subsequent attachment of haptens or labels to the peptide" (e.g., see Mrksich Declaration, paragraph 14).

[6] Applicants argue, "Brinkley teaches the use of protecting groups, wherein 'the N-terminal amino group is N-acylates [i.e., protected]'. However, the examiner fails to recognize that this use of a protecting group is unrelated to the use of protecting groups in the claims of the application under review. In Brinkley, the acetyl protecting group serves to block the N-terminal

amine from any subsequent chemical reactions ... [which] is not useful for subsequent attachment of labels or haptens at the N-terminal amine group" (e.g., see Mrksich Declaration, paragraph 15).

[7] Applicants argue, "It is significant that all of the examples in Brinkley involve the attachment of labels and haptens to peptide carriers that have already been formed, and does not discuss the direct incorporation of a label or hapten during the solid-phase synthesis" (e.g., see Mrksich Declaration, page 4, paragraph 16).

[8] Applicants argue, "Binkley emphasizes methods that can be used to control the degree of labeling of a peptide carrier with labels or haptens. Brinkley recognizes that 'when proteins are labeled with fluorescent dyes, the fluorescence increase as more dyes are added; at the same time, however, the fluorescence efficiency decreases as a result of the quenching ...' Brinkley goes on to describe strategies for optimizing the amount of dyes that are attached to each peptide carrier. This emphasis in the reference clearly teaches away from the concept of using a peptide carrier that has labels and haptens attached at predetermined positions" (e.g., see Mrksich Declaration, pages 4 and 5, paragraph 16).

[9] Applicants argue, "the motivation to use Merrifield's solid-phase technology is without basis" (e.g., see Mrksich Declaration, page 5, paragraph 18).

[10] Applicants argue, "In hindsight, the Examiner's arguments can be interpreted in a manner that is consistent with the Office Action, but at the time of the invention, this argument calls for a level of insight and expertise that were very clearly beyond one of ordinary skill in the art" (e.g., see Mrksich Declaration, pages 5 and 6, paragraph 19).

This is not found persuasive for the following reasons:

[1] Merrifield is no longer being applied and, as a result, Applicants' arguments are moot. Yang et al. explicitly teach how to make the insulin A-chain using solid-phase synthesis and Bredehorst et al. explicitly teach how to modify this insulin A-chain to attach the DNP and Fl side groups.

[2] The Declaration under 37 CFR § 1.132 filed December 5, 2005 is sufficient to overcome the rejection of claims 33-39 based upon the newly amended Bredehorst et al. rejection. To the extent that the Declaration can be applied to the newly cited rejection, the following points are noted:

First, the Examiner concedes that Dr. Milan Mrksich is unquestionably an expert in the field of organic chemistry and a highly distinguished member of the scientific community. However, that is not the end of the inquiry. "[I]n assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion." (e.g., see MPEP § 716.01(c)). Here, Applicants provide no factual evidence. The interest of the expert in the outcome is great (i.e., it's the expert's application at issue). The opposing evidence is strong for the reasons stated in the newly amended rejection above. Finally, the nature of the matter, which Applicants are trying to establish, pertain only to legal conclusions (e.g., no motivation, etc., see sections **[3]-[10]** below, which is incorporated in its entirety herein by reference) that have been set forth in an entirely conclusory manner and thus should be afforded little or no weight (e.g., see In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement").

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

[3] In response to applicant's arguments against the Bredehorst et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined reference clearly teach the use of solid phase synthesis (e.g., see Yang et al., abstract wherein insulin A-chain was produced using solid-phase synthesis). Furthermore, Dr. Mrksich provide no evidence to support the assertion that "... had the authors [in Bredehorst] appreciated that solid phase synthesis could be used to prepare the carrier, they would have done so" (e.g., see Mrksich Declaration, page 4, paragraph 12). This is mere speculation.

[4] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., solid-phase synthesis of a carrier from amino acids that are covalently bound to labels or haptens) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here independent claim 33 merely requires that the linear carrier be formed using solid-phase synthesis. The claim does not require that the hapten, luminescent chelate, or biotin be produced by solid phase synthesis.

[5 and 9] The Merrifield references is not longer being applied and, as a result, Applicants' arguments are moot.

[6] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "for use in the subsequent attachment of labels or haptens") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). That is, Applicants use of "comprising" terminology does not preclude the use of "intermediate" method steps. For example, the combined references teach the use of additional amino acids with protected side groups (e.g., see Yan et al., abstract wherein "tert-Bu" protection of side chains is used and also Fmoc protection is used for the N-terminus). For example, the DNP/Fluoescein groups in Bredehorst could not be "subsequently" added to the insulin without first removing these protecting groups.

[7] Again, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "direct incorporation") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). That is, Applicants' use of "comprising" terminology does not preclude the claims from reading on "indirect" embodiments.

[8] "[A] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be lead in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend upon the particular facts; in general, a reference will

teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (citing United States V. Adams, 383 U.S. 39, 52, 148 USPQ 478, 484 (1966)). Here, Binkley has simply acknowledged that quenching can be a problem. This does not represent a teaching away from the Brodehorst et al., for example, because Brodehorst et al. also recognize that quenching can be a problem and cite a specific methodology for avoiding this problem (e.g., see page 277, column 2, paragraph 1, The backbone of the carrier is the A-chain of insulin which provides several essential features, including ... (c) sufficient length between the label attachment sites to prevent self-quenching of the fluorophores). Furthermore, a reference that "teaches away" does not per se preclude a *prima facie* case of obviousness, but rather the "teaching away" of the reference is a factor to be considered in determining unobviousness. Id 27 F.3d at 552, 31 USPQ 2d at 1132. Thus, even if, assuming arguendo, Brinkley did represent a teaching away (which is not the case), it would not outweigh the other factors stated in the above rejection.

[10] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In addition, the Examiner notes that Applicants' provide no evidence for this assertion and the present references used in the above 35 U.S.C. § 103(a)

rejection support a contrary view. Solid-phase synthesis was widely known and practiced routinely by persons of ordinary skill in the art and had in fact been used to produce insulin A-chain like the insulin A-chain used by Bredehorst. Furthermore, Bredehorst disclose facile methods for modifying the insulin A-chain with haptens and fluorophores. Thus, the evidence of record does not support Applicants' assertions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 17, 2006

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